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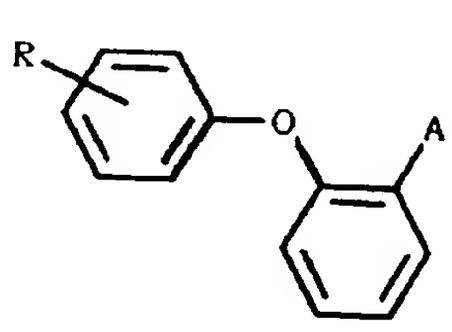
(54) Phenoxyphenyl derivatives.

(57) The invention concerns a phenoxyphenyl derivative having the formula



(I)

wherein
R is one or two halogen atoms; and
A is $CH_2NR_1R_2$ or 4,5-dihydro-1H-imidazole, in which R_1 and R_2 are independently selected from hydrogen and lower alkyl; or
a pharmaceutically acceptable salt thereof.

The compounds have long half-lives and can be used against depression.

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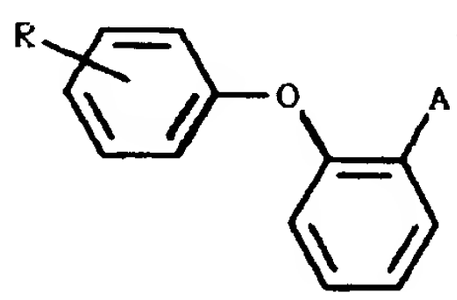
The invention concerns phenoxyphenyl derivatives, their preparation, pharmaceutical preparations containing the same, and their use for the preparation of a medicament.

Derivatives having chemical structures related to the phenoxyphenyl derivatives of this invention are known from J. Jilek et al., Collect. Czech. Commun., 54, 1995 (1989), from J. Jilek et al., *ibid*, 54, 3294 (1989), from Czech Patent Application 151,755, and from European Patent Application 402,097. These references disclose phenylthiophenyl derivatives being selective serotonin reuptake inhibitors. It was found that these prior art compounds have short half-lives, which is a serious drawback in their practical use. The compounds of the present invention, however, have long half-lives and, apart from inhibition of the reuptake of serotonin, also inhibit the reuptake of noradrenaline and dopamine. The dopamine reuptake inhibition is thought to produce a fast elevation of mood, which makes the compounds suitable for the acute relief of symptoms in depression. This is considered to be a substantial advantage over known antidepressant drugs, like specific serotonin reuptake blockers, which have a delayed onset of action of two weeks or more. Moreover, the present compounds, because of their dopamine reuptake blocking properties, are less sedative than the prior art compounds, and thus more appropriate in the treatment of depressive patients with psychomotor retardation. The compounds of the invention can also be used to treat Parkinsons disease, obesity, anxiety disorders, central pain, addiction, and negative symptoms in schizophrenic patients.

The phenoxyphenyl derivatives of this invention have the formula



(I)

wherein
R is one or two halogen atoms; and
A is $CH_2NR_1R_2$ or 4,5-dihydro-1H-imidazole, in which R_1 and R_2 are independently selected from hydrogen and lower alkyl; or
a pharmaceutically acceptable salt thereof.

Preferred compounds according to this invention are phenoxyphenyl derivatives according to formula I, wherein R is one or two chlorine atoms, or a pharmaceutically acceptable salt thereof.

The phenoxyphenyl derivatives of formula I, wherein A is CH_2NH_2, $CH_2N(CH_3)_2$, or 4,5-dihydro-1H-imidazole, and preferably wherein, moreover, R is one or two chlorine substituents, or a pharmaceutically acceptable salt thereof, are even more preferred.

The most preferred phenoxyphenyl derivatives are 2-(3,4-dichlorophenoxy)benzenemethanamine and 2-[2-(4-chlorophenoxy)phenyl]-4,5-dihydro-1H-imidazole, or pharmaceutically acceptable salts thereof.

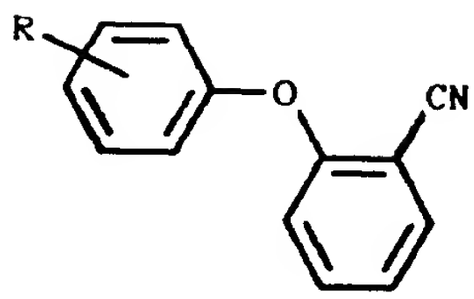
The term lower alkyl, used in the definition of the phenoxyphenyl derivatives having formula I, means a branched or unbranched alkyl group having preferably 1-6 carbon atoms, such as methyl, ethyl, propyl, isopropyl, butyl, *tert*-butyl, pentyl, hexyl and the like. Preferred alkyl groups have 1-4 carbon atoms, and most preferred is the methyl group.

The term halogen used in the definition of formula I means fluorine, chlorine, bromine or iodine. Chlorine is the preferred halogen.

The novel compounds of formula I may be isolated from a reaction mixture in the form of a pharmaceutically acceptable salt. The pharmaceutically acceptable salts may also be obtained by treating the free base of formula I with an organic or inorganic acid such as HCl, HBr, HI, H_2SO_4, H_3PO_4, acetic acid, propionic acid, glycolic acid, maleic acid, malonic acid, methanesulphonic acid, fumaric acid, succinic acid, tartaric acid, citric acid, benzoic acid, pamoic acid, or ascorbic acid.

The phenoxyphenyl derivatives according to this invention can be prepared by methods known for analogous compounds.

A suitable method of preparation is a condensation of a nitrile having the formula

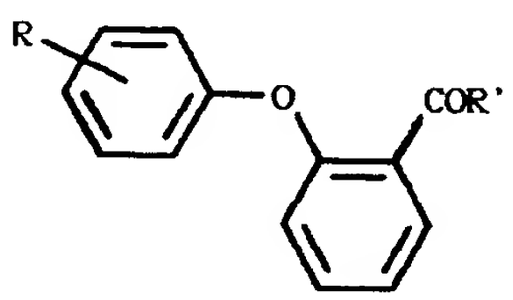


(II)

wherein R has the previously given meaning, with 1,2-ethanediamine, optionally followed by conversion into a pharmaceutically acceptable salt; or a reduction of the nitrile having formula II, optionally followed by alkylation and/or conversion into a pharmaceutically acceptable salt.

The nitrile having formula II can be prepared by condensation of 2-halobenzonitrile, and preferably 2-bromobenzonitrile, with a mono- or dihalo substituted phenol under alkaline conditions. The nitrile may also be prepared by condensation of 2-hydroxybenzonitrile and a bis[mono- or dihalobenzene]iodonium salt, which can be obtained from mono- or dihalobenzene, iodine, and a mixture of sulfuric and nitric acid.

The phenoxyphenyl derivative of formula I having A is $CH_2NR_1R_2$, wherein R_1 and R_2 have the previously given meanings, can also be prepared by reduction of an amide having formula



(III)

wherein R has the previously given meaning, and R' is NR_1R_2, in which R_1 and R_2 have the previously given meanings.

Compounds of formula I having A is 4,5-dihydro-1H-imidazole can also be prepared from a nitrile having formula II through a Pinner reaction giving an imino ester, which can be converted into the 4,5-dihydro-1H-imidazole by 1,2-ethanediamine.

Condensation of 1,2-ethanediamine with acids or esters having formula III, wherein R has the previously given meaning and R' is hydroxy, or methoxy or another lower alkoxy, also gives the desired phenoxyphenyl derivative having A is 4,5-dihydro-1H-imidazole. Lower alkoxy means an alkoxy group of which the alkyl moiety is a lower alkyl group as previously defined.

Phenoxyphenyl derivatives of formula I having A is $CH_2NR_1R_2$ can be prepared from acids or esters of formula III by reduction to the corresponding alcohol, conversion of the hydroxy group into a suitable leaving group, such as chlorine or bromine, and condensation with an amine having the formula HNR_1R_2, wherein R_1 and R_2 have the previously given meanings.

It is possible to convert the products obtained by one of the previously mentioned procedures into another product according to the invention. Using generally known methods it is, for instance, possible to convert compounds wherein R_1 and/or R_2 is hydrogen, e.g. by a Leuckart-Wallach reaction, into compounds wherein R_1 and/or R_2 is alkyl.

The compounds of the invention may be administered enterally or parenterally, and for humans preferably in a daily dosage of 0,001-10 mg per kg body weight. Mixed with pharmaceutically suitable auxiliaries, e.g. as described in the standard reference, Chase et al., Remington's Pharmaceutical Sciences, the compounds may be compressed into solid dosage units, such as pills, tablets, or be processed into capsules or suppositories. By means of pharmaceutically suitable liquids the compounds can also be applied as an injection preparation in the form of a solution, suspension, emulsion, or as a spray, e.g. a nasal spray.

The invention is further illustrated by the following examples.

Example 1

2-(4-chlorophenoxy)benzenemethanamine hydrochloride

A solution of 51.4 g of 4-chlorophenol in 500 ml of dry N,N-dimethylformamide (DMF) was added to a suspension of 20 g of 60% sodium hydride in 800 ml of dry DMF under nitrogen. After 30 min at 25 °C, 1 g of 18-crown-6 was added. After the addition of 73 g of 2-bromobenzonitrile in 500 ml of dry DMF, the mixture was heated at 100 °C for 16 h. After concentration *in vacuo*, 2N sodium hydroxide and ethyl acetate were added. The organic layer was separated, washed with 2N sodium hydroxide and water, dried over magnesium sulfate, and evaporated to dryness. The residue was recrystallized from methanol to give in 60% yield 2-(4-chlorophenoxy)benzonitrile. To a suspension of 6 g of lithium aluminum hydride in 100 ml of dry tetrahydrofuran (THF) were added under nitrogen 20 g of 2-(4-chlorophenoxy)benzonitrile. The mixture was heated at reflux for 3 h, cooled, and 25 ml of 1N sodium hydroxide were added dropwise. The precipitate formed was filtered off and washed with diethyl ether. The filtrate was evaporated to dryness, dissolved in ethyl acetate and acidified with a saturated solution of hydrochloric acid in ethanol. The precipitate was collected and recrystallized from ethanol to give in 95% yield 2-(4-chlorophenoxy)-benzenemethanamine hydrochloride. mp 253 °C.

Example 2

2-(3,4-dichlorophenoxy)benzenemethanamine hydrochloride

To a vigorously stirred solution of 12.7 g of iodine in 13 ml of 60% fuming sulfuric acid and 33 ml of concentrated sulfuric acid, was added dropwise a solution of 7.5 ml of 90% fuming nitric acid, 1.9 ml of 60% fuming sulfuric acid, and 5.5 ml of concentrated sulfuric acid. The mixture was stirred for 2 h at 70-80 °C. After cooling to 0 °C, a solution of 28.2 ml of 1,2-dichlorobenzene was added under vigorous stirring. The reaction mixture was kept at 45 °C for 2 h, cooled to 0 °C, and 100 ml of cold water were added at once. The aqueous layer was decanted, the residue, dissolved in methanol, and 5 ml of concentrated hydrochloric acid were added. The precipitate, after filtration and washing with methanol, was dried, and 24.4 g of this precipitate were added to a solution of 5.6 g of 2-hydroxybenzonitrile and 2.2 g of sodium hydroxide in 440 ml of water. After 22 h of reflux, the mixture was cooled and extracted with diethyl ether. The organic layer was washed with 2N sodium hydroxide, dried over magnesium sulfate, and evaporated to dryness. The residue was recrystallized from diethyl ether to give in 80% yield 2-(3,4-dichlorophenoxy)-benzonitrile.

A solution of 10 g of anhydrous aluminum chloride in 150 ml of dry diethyl ether was added dropwise under nitrogen to a suspension of 3.1 g of lithium aluminum hydride in 150 ml of dry diethyl ether, and the mixture was cooled at 0 °C. After 30 min at 0 °C, a solution of 5.0 g of 2-(3,4-dichlorophenoxy)benzonitrile in 150 ml of dry diethyl ether was added slowly. The mixture was stirred for 24 h at 25 °C, and a concentrated aqueous solution of sodium hydrogen carbonate was added. The precipitate was filtered off, the filtrate was evaporated to dryness, dissolved in ethyl acetate, and acidified with a concentrated solution of hydrochloric acid in ethanol. The precipitate was collected and recrystallized from a mixture of ethanol and diethyl ether, to give in 75% yield 2-(3,4-dichlorophenoxy)benzenemethanamine hydrochloride. mp 213 °C.

Example 3

By addition of an aqueous solution of the disodium salt of pamoic acid to a solution of the compound of example 2 in ethanol, was prepared 2-(3,4-dichlorophenoxy)benzenemethanamine 4,4'-methylenebis[3-hydroxy-2-naphthalenecarboxylic acid] (2:1) salt. mp 230 °C.

Example 4

2-(4-chlorophenoxy)-N,N-dimethylbenzenemethanamine (Z)-2-butenedioate

A mixture of 5 g of 2-(4-chlorophenoxy)benzenemethanamine (Example 1), 50 ml of formic acid, and 50 ml of a 37% solution of formaldehyde in water was heated at 100 °C for 3 h. The solution was cooled, made alkaline with sodium hydroxide, and extracted with dichloromethane. The organic layer was washed with brine, dried over magnesium sulfate, and evaporated to dryness. The residue was dissolved in ethanol and maleic acid was added. After dilution with diethyl ether, the precipitate was collected, washed with diethyl ether and dried, to give in 80% yield 2-(4-chlorophenoxy)-N,N-dimethylbenzenemethanamine (Z)-2-butenedioate. mp 118 °C.

Example 5

2-[2-(4-chlorophenoxy)phenyl]-4,5-dihydro-1H-imidazole (Z)-2-butenedioate

A solution of 20 g of 2-(4-chlorophenoxy)benzonitrile (Example 1) in 80 ml of 1,2-ethanediamine was saturated with hydrogen sulfide during 30 min at 0 °C. The mixture was stirred at 25 °C for 4 days, concentrated, and ethyl acetate was added. The organic layer was washed with 2N sodium hydroxide, dried over magnesium sulfate, and evaporated to dryness. The residue was dissolved in ethanol, treated with maleic acid, and recrystallized from ethanol to give in 80% yield 2-[2-(4-chlorophenoxy)phenyl]-4,5-dihydro-1H-imidazole (Z)-2-butenedioate. mp 207 °C.

Example 6

In an analogous manner, as described in Example 5, were prepared:

a. 2-[2-(3,4-dichlorophenoxy)phenyl]-4,5-dihydro-1H-imidazole (Z)-2-butenedioate. mp 123 °C.

b. 2-[2-(4-chlorophenoxy)phenyl]-4,5-dihydro-1H-imidazole 4,4'-methylenebis[3-hydroxy-2-naphthalenecarboxylic acid] (2:1) salt. mp >250 °C.

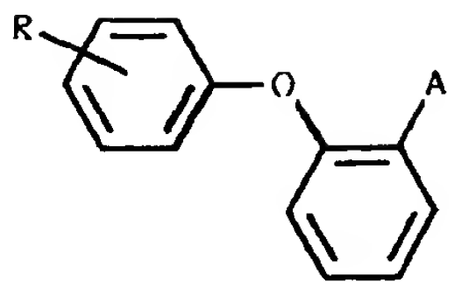
Example 7

The biological half-lives of the phenoxyphenyl derivatives were determined for the sleep-wake behaviour in rats and compared with the half-lives of the prior art compounds.

Product of Example	half-life in h
1	1-2.5
2	2.5
4	1
5	3
6a.	1.5-2.5
prior art:	
2-(phenylthio)benzenemethanamine	0.5
2-[(4-methoxyphenyl)thio]-benzenemethanamine	<0.5

Claims

1. A phenoxyphenyl derivative having the formula



(I)

wherein
R is one or two halogen atoms; and
A is $CH_2NR_1R_2$ or 4,5-dihydro-1H-imidazole, in which R_1 and R_2 are independently selected from hydrogen and lower alkyl; or
a pharmaceutically acceptable salt thereof.

2. The phenoxyphenyl derivative of claim 1, wherein R is one or two chlorine atoms, or a pharmaceutically acceptable salt thereof.

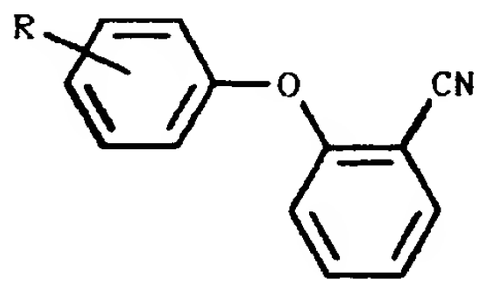
3. The phenoxyphenyl derivative of claim 1 or 2, wherein A is CH_2NH_2, $CH_2N(CH_3)_2$, or 4,5-dihydro-1H-imidazole, or a pharmaceutically acceptable salt thereof.

4. 2-(3,4-dichlorophenoxy)benzenemethanamine or a pharmaceutically acceptable salt thereof.

5. 2-[2-(4-chlorophenoxy)phenyl]-4,5-dihydro-1H-imidazole or a pharmaceutically acceptable salt thereof.

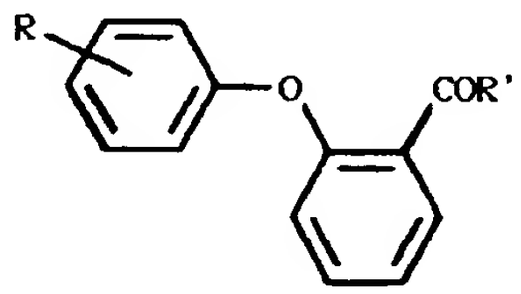
6. The phenoxyphenyl derivative of any one of claims 1-5 for use in therapy.

7. A process for the preparation of the phenoxyphenyl derivative of claim 1, characterized in that a nitrile having the formula



(II)

wherein R has the previously given meaning, is condensed with 1,2-ethanediamine, or is reduced, optionally followed by alkylation;
or alternatively, when A is $CH_2NR_1R_2$, that an amide having the formula



(III)

is reduced; after which the compound obtained may optionally be converted into a pharmaceutically acceptable salt.

8. A pharmaceutical preparation containing the phenoxyphenyl derivative of claim 1 in admixture with pharmaceutically acceptable auxiliaries.

9. A use of the phenoxyphenyl derivative of claim 1 for the manufacture of a medicament with a long half-life and activity against depression.

European Patent Office

EUROPEAN SEARCH REPORT

Application Number

EP 92 20 1484

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. Cl.5)
A,D	COLLECTION OF CZECHOSLOVAK CHEMICAL COMMUNICATIONS, vol. 54, no. 7, 1989, PRAGUE CS pages 1995 - 2008; J. JILEK: 'POTENTIAL ANTIDEPRESANTS: 2-(PHENYLTHIO)ARALKYLAMINES' * page 1995 - page 2000 *	1-9	C07C217/58 A61K31/135 C07D233/22
A	DE-A-2 807 623 (SCIENCE UNION ET CIE.) * claims *	1-9	
A	DE-A-2 418 502 (SCHERING A.G.) * claims *	1-9	
A	DE-A-2 047 677 (MERCK & CO. INC.) * page 1 - page 4; claims *	1-9	
A	GB-A-1 187 200 (DOW CHEMICAL COMPANY) * claims *	1-9	

TECHNICAL FIELDS SEARCHED (Int. Cl.5)

C07C
C07D

The present search report has been drawn up for all claims

Place of search	Date of completion of the search	Examiner
THE HAGUE	04 SEPTEMBER 1992	SANCHEZ GARCIA J.M.

CATEGORY OF CITED DOCUMENTS

X : particularly relevant if taken alone
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